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(54) Abstract Title
Sterilisation of pharmaceuticals

(57) A method of sterilising a pharmaceutical composition containing a suspension of a pharmaceutical comprises rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

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(54) Title: STERILISATION OF PHARMACEUTICALS

(57) Abstract: A method of sterilising a pharmaceutical composition containing a suspension of a pharmaceutical comprises rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

STERILISATION OF PHARMACEUTICALS

The present invention concerns a method for the sterilisation of drugs, in particular suspensions of drugs intended for use in nebulizers.

Previously it was acceptable for drugs intended for use in nebulizers to be prepared under "clean" conditions. Recently, however, the US FDA has implemented a requirement for all nebulizer solutions to be sterile.

In the light of the US FDA decision it is necessary to produce sterile suspension drugs in the US. This is emphasised by problems which have resulted from the use of "clean" suspensions. Multidose formulations made under "clean" conditions in which the composition was in a "preserved" state were previously acceptable in the US. However such preserved and clean-filled formulations have caused fatalities in the US due to contamination.

A method of sterilising dry, powdered budesonide is known from International Publication Number WO 99/25359. The method of sterilisation requires budesonide powder to be sterilised and then be mixed with the other components of the formulation under sterile conditions. The drug formulation is subsequently made up under sterile conditions. This method does not permit the complete formulation to be sterilised immediately prior to dispensing into the final sterile vessel.

The sterilisation of suspensions raises particular problems. The desired biological activity of the formulation commonly requires that the diameter of particles of the drug lies within a narrow range (typically less than 5 micrometres). The standard means of sterilisation, that is the raising of the temperature of the formulation to 121°C for 15 minutes, frequently destroys one or more of the components of the formulation. In addition this treatment results in the clumping or agglomeration of the drug particles in the suspension such that the efficacy of the resulting product is impaired or abolished.

Known alternative methods for the sterilisation of pharmaceuticals are inappropriate for sterilizing suspension formulations of drugs. Pharmaceuticals

may be sterilised by passage though a filter having a pore size of not more than 0.2 micrometres. However this cannot be used in the case of many suspensions as the required particle size in these formulations is significantly greater than this filter pore size. Similarly, pharmaceuticals may generally be sterilised by gamma-irradiation, but budesonide, for example, is destroyed by such treatment. No further methods for the sterilisation of pharmaceuticals are currently acceptable to regulatory agencies.

An object of the present invention is to provide an alternative and/or an improved method for sterilization of suspensions of pharmaceuticals.

Accordingly, the present invention provides a method of sterilising a pharmaceutical composition, which composition is or contains a suspension of a pharmaceutically active agent, comprising rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

The heating process is carried out to achieve sterilization of the composition, whilst avoiding such excessive heating that unacceptable damage or deterioration to the composition occurs. A number of known pharmaceutically active agents are heat-sensitive, thus rendering them difficult to sterilize using hitherto known procedures. The present invention utilizes heat treatment that combines high temperature but short duration with the result that effective sterilization is obtained without adversely affecting the integrity or other physical characteristics of the active agent.

In a use of the invention, a suspension of a glucocorticosteroid, that is to say a suspension in water plus surfactant, in a liquid form, has been heated from room temperature to about 140 degrees C, held around this temperature for 5 to 6 seconds and then rapidly cooled back to room temperature. Inspection of the suspension afterwards showed no apparent deterioration, and calculation of the kill rate, used to assess whether sterilization has been successful, confirmed a kill rate comfortably above 10, this value being regarded as the threshold for a sterilizing process.

The principle of high temperature short time treatment of liquids, in particular

ultra high temperature processing of milk is described in particular in H. Burton, Ultra-High-Temperature Processing of Milk and Milk Products (Elsevier Applied Science Publishers Ltd 1988). In addition, there is a discussion of ultra high temperature sterilisation of milk in Ullmann's Encyclopaedia, 5th edition, 1998 vol. A11, pages 549-552, and apparatus suitable for carrying out the high temperature short time processing methods used in the present invention is described therein.

The increase in temperature is preferably extremely rapid so that the composition is heated very quickly to a sterilizing temperature without spending unnecessary time at intermediate temperatures at which little or no sterilizing can occur but heat damage can. The step of increasing the temperature of the composition from the ambient temperature to the elevated temperature typically takes less than 10 seconds, less than 5 seconds, preferably less than 2 seconds.

Similarly, decreasing the temperature is also done rapidly for the same reasons, and typically the step of decreasing the temperature of the composition from the elevated temperature to ambient temperature takes less than 10 seconds, less than 5 seconds, preferably less than 2 seconds.

Good results have been seen by heating a suspension to the elevated temperature in around 1 second, and decreasing the temperature to ambient also in around 1 second.

The elevated temperature used in the method is sufficient to achieve sterilization before significant damage can be done to the composition. Suitable elevated temperatures are above about 130°C, more suitably above 135°C and preferably at about or exceeding 140°C. In examples of the invention described below in more detail, good results have been obtained at temperatures of about 144 to 145°C. The ranges suitable may vary from one composition to the next and therefore the precise temperatures chosen can be adapted from the specific ranges mentioned whilst achieving the same result of sterilization without damaging the resulting composition.

In use of the invention, it is found that the kill rate of bacteria increases exponentially with temperature and while the rate of degradation of active ingredient in, say, a pharmaceutical that is being treated according to the invention is also increased with increase in temperature, the increase in

The invention further provides a method of treating a pharmaceutical composition to reduce its microbial load, comprising rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature. The method preferably comprises sterilization of the composition as described above.

In another aspect, the invention provides a method of sterilising a concentrated formulation for use in a pharmaceutical composition, comprising rapidly heating the concentrated formulation from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the concentrated formulation to ambient temperature. The sterilization is preferably carried out as described above.

Examples of concentrated formulations that can be sterilized include a pharmaceutical agent and a surfactant; a suspension of a drug in water or another solvent; a suspension of a drug in a surfactant solution. Once sterilized, these concentrates can be stored or used immediately or after an interval for preparation of formulations at the working concentration of the drug concerned.

A still further aspect of the invention lies in a method of sterilising a pharmaceutical composition, characterized in that the sterilization is carried out by "square wave heating" and in that the sterilization is carried out continuously. The square wave heating suitably comprises rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

The square wave heating treatment according to the invention preferably comprises an elevated hold temperature at which sterilisation but substantially no degradation of the composition occurs, and which temperature is generally in the range of 130°C or more, preferably 135°C and more preferably 140°C or higher. The hold temperature is generally held for a period in excess of 1 and less than 20 seconds, more preferably in the range 2 to 10 seconds.

A particular advantage of this aspect of the invention is that the sterilization can be continuous and can be carried out in combination with other steps in

degradation has a different, specifically a smaller, co-efficient. The method of the invention hence takes advantage of this by operating at a high temperature for a short period of time to achieve the bacteria kill necessary for sterilisation but avoiding unacceptable damage to the chemical components of the composition.

Using a hold temperature of at or around 150°C or higher produces exceptionally rapid bacteria kill, with little collateral damage to other components of a pharmaceutical composition, such as the active ingredient and its carrier. A rapid rise up to this temperature, in a period of about one or two seconds, can be achieved using pumps operating at speeds sufficiently fast to pump the liquid composition through heating pipes up to the desired hold temperature. However, if acceptable sterilisation can be achieved at a lower hold temperature such as at or around 140°C, using pumps operating at a slower speed, and without cause of unacceptable damage to the pharmaceutical composition, then this balance of slightly lower temperature and slightly lower pump speed is generally preferable to excessively high pump speeds.

The duration of the elevated temperature step can also vary, and as described above the method is carried out to achieve a sterile end product without causing damage to the composition. Suitable durations are from about 2 to about 20 seconds, preferably from about 3 to about 10 seconds. These duration may also vary from one composition to the next. They may in addition vary according to the concentration of the particular components of the composition.

By reference to ambient temperature is generally meant reference to room temperature, in the range of about 15-25°C. However, reference to ambient temperature in terms of the temperature from which the composition being treated is raised to elevated temperature and to which the heated composition is cooled is intended to refer not to a specific temperature or specific range of temperatures but instead to any temperature at which the composition is substantially stable for long periods of time and is not adversely effected by being maintained at that temperature for a long period of time.

Pharmaceutical suspensions that can be sterilized according to the methods described herein are more or less without limit, though the method is particularly suitable for compositions including a drug in suspension, water or another solvent and, optionally, surfactants and/or preservatives.

preparation of the end product, such as particle size monitoring and adjustment, packaging, labelling, etc. For example, the method can further comprise dispensing sterilized pharmaceutical composition into storage vessels and sealing the storage vessels in a continuous process. The "blow-fill-seal" method is a packaging method that can be used in the invention, and typical storage vessels are selected from pre-sterilised ampoules, typically of plastic, metal or glass.

Where concentrates are sterilized, the method optionally includes diluting a sterile concentrate by a bulk composition under sterile conditions prior to dispensing into storage vessels.

Also provided in the invention are pharmaceutical compositions sterilised by the methods of the invention. Specifically, the invention provides a sterile suspension of a steroid obtainable by sterilizing a steroid suspension according to the invention, more particularly a sterile suspension of budesonide obtained by sterilizing a budesonide suspension according to the methods of the invention.

In a specific embodiment of the invention, a formulation comprising budesonide particles less than 5 μm in diameter, a polysorbate surfactant, water and preservatives which may include benzylkonium (bkc) and ascorbic acid has been sterilized by this method. Alternatively a concentrate of budesonide and polysorbate surfactant can be sterilised by this method prior to mixing with the remaining components of the complete formulation. Budesonide and other drugs that are formulated as suspensions can also be sterilized as a dispersion without surfactant present. Such treatment has been found not to result in the degradation of potentially heat-sensitive components of the formulation, and to enable production of sterilized suspensions having particles in a size range acceptable for pharmaceutical use.

Where a portion of the product of the invention has particles outside a given size range then it is optional to further process this product, for example to filter or otherwise remove particles of undesired size or to convert those particles into a desired size range. One way to carry out a particle size conversion is to use a micronizing device, conveniently as a component of the sterile production line, and a suitable device, referred to as a Microfluidizer (®), is available from Microfluidics, Inc, described in WO 99/07466. Another way is to use a filter with a cut-off point to filter out particles in the suspension above a certain size. For

inhalation purposes, a filter removing particles above about 10μm may be used, for example.

The effectiveness of the treatment of the invention is unexpected as treatment at 140°C would be expected to require minutes, not seconds, as the standard treatment requires 15 minutes at 121°C to achieve sterility. Furthermore, such high temperatures would be expected to damage the formulation or drug substance. It is reported in WO 99/25359 (Astra) that long exposure of budesonide to high temperatures leads to agglomeration of the finely divided particles - the sterilisation of budesonide is generally considered by the market to be impossible. Analysis of product of the invention has confirmed its chemical stability more than one month afer sterilization.

This method of sterilisation of pharmaceuticals may be applied to complete suspensions and to concentrates thereof. One application is the sterilisation of asthma drugs. These may be sterilised by conventional terminal sterilisation. However, the polymeric ampoules for such drugs must be able to be squeezed and such ampoules are not heat-resistant. Thus conventional blow-fill seal methods are not applicable in this context. The method of the invention allows such difficulties to be overcome.

The method of sterilisation described has several advantages over previous methods of sterilising pharmaceuticals. This method substantially does not damage the drug and allows the sterilisation of a product for which this was previously believed not to be possible. The method removes the need to filter sterilise the bulk component of the formulation. Indeed, filter sterilisation is not an absolute assurance of sterility as the integrity of the filter cannot be constantly monitored throughout the filling process. The use of high temperature / short time sterilization, therefore, can provide more effective sterilization than that resulting from filtration. The cost of this process may also be reduced by eliminating the requirement for expensive filters.

This method allows entire drug formulations or their component parts to be sterilised in line immediately prior to filling. The method is quick, and can be applied to an entire batch of formulation. In addition the method could be applied to the continuous production of a drug formulation. Further to this, high temperature / short time sterilization can be monitored throughout the filling

process by validated thermocouple and flow rate recording to provide an absolute assurance of sterility. Analysis of products obtained in the specific embodiments have shown these to be sterile. Once sufficient data has been gathered for a given product, such monitoring allows batches of the product to be released for sale without waiting for the results of tests to confirm sterility. This reduces the cost and time delay presently incurred while awaiting the results of sterility release testing.

The invention is now illustrated in specific embodiments by way of the following examples and with reference to Table 1 which shows results of the sterilization method of the invention.

Example 1: Preparation of a "clean" budesonide formulation

Preparation of a clean suspension of budesonide particles for use in a nebulizer in which the final formulation comprises budesonide, a polysorbate surfactant, water and preservatives was carried out as follows.

A bulk solution consisting of all the components of the final formulation except budesonide and the surfactant was sterilised by passage through a 0.2μm filter (0.1μm is also suitable). The filtered solution was held at room temperature and a pressure of approximately 2 bar in a sterile vessel.

In the enclosed environment of a container cabinet, the polysorbate surfactant was filter sterilised into a sterile vessel. To this vessel micronised budesonide was added aseptically. The particle size of the budesonide was such that 100% of the particles were less than 10μm and 95% of the particles were less than 5μm in diameter. After addition the budesonide lay on top of the filtered polysorbate. Mixing was achieved by the use of a high shear mixing shaft. Twenty to twenty-five minutes of continuous mixing were required for the budesonide to go completely into suspension. After mixing was complete the mixing shaft was rinsed with sterile water and the vessel was sealed.

The complete formulation was produced by adding the budesonide/polysorbate concentrate to the bulk solution in a laminar flow hood after which the vessel was capped. A paddle at the bottom of this vessel rotating at approximately 700 rpm

was required to maintain the suspension. The resulting formulation was dispensed to the final vessels under "clean" conditions.

This method results in a formulation that was "clean", but not sterile. The bioburden of the formulation was not increased during the process. The final bioburden of the formulation was required to be less than 10 CFU / 100ml.

Example 2: Sterilization of a budesonide formulation

The formulation to be sterilised was passed through narrow lines of pharmaceutical quality stainless steel in which the sample was rapidly raised to an elevated temperature, maintained at this holding temperature for a period of time, then rapidly returned to ambient temperature. Parameters described in Table 1 are the BMRT (bulk mean retention time), that is the time between the sample being raised above ambient temperature and being returned to ambient temperature, and the FFERT, the time for which the sample is maintained at the elevated temperature. The BMRT always exceeds the FFERT by a small margin, hence the term square wave heating. The theoretical kill rate, Fo, may be calculated from the FFERT and the elevated temperature. The value of Fo is optimally greater than 10, but values greater than 8 are acceptable for the production of sterile formulations.

Ten litres of cleanly made budesonide solution, produced as in Example 1, was mixed in a bowl and four samples were run through the test rig. The data obtained showed that two sets of conditions resulted in values of Fo that were significantly greater than the required value of 10. Run 1 gave a Fo value of 19.9 with a temperature of 143.9°C and a FFERT of 5.4s. Run 4 gave an Fo of 24.1 with a hold temperature of 144.8°C and a FFERT of 5.4s. Runs 2 and 3 employed a lower hold temperature and did not give an acceptable value of Fo.

The results are shown in the following table 1.

Hold conditions analysis	Run 1	Run 2	Run 3	Run 4
Hold temperature °C	143.9	133.0	139.4	144.8
Hold time BMRT (seconds)	7.5	9.4	6.9	7.5
Hold time FFERT (seconds)	5.4	6.7	4.5	5.4
Legal Hold Fo (Kill factor)	19.9	2.5	4.7	24.1

In addition to producing the required Fo, the conditions employed did not appear to alter the physical properties of the formulation.

Example 3: Purity testing of a sterilized budesonide formulation

Chromatographic purity testing of budesonide suspension for nebulization, sterilized according to Example 2 was carried out to assess whether the treatment of Example 2 results in an increase of non-biological impurities in the samples. The proportions of budesonide-related compounds and unknown compounds in multiple samples from each test run of Example 2 were calculated, as was the %LC, a measure of degradation. In all cases, the values from the samples and the controls, which had not been subjected to the method of Example 2, were in significant agreement, both being less than 0.1%. This indicated that the process used for high temperature / short time sterilisation did not result in an increase in the levels of impurities in the budesonide formulation.

Example 4 (comparative): Attempt to sterilise a budesonide suspension with high intensity light

An alternative method of sterilization of a budesonide suspension is treatment with high intensity light. The so-called "Pure-bright" process allows treatment with light at 900 times the intensity of sunlight at sea level. Attempts to sterilize budesonide formulations produced as in Example 1 resulted in the destruction of the budesonide. Although such a process might be expected to sterilise budesonide suspensions, the data clearly show that this method is not appropriate in that the drug is completely destroyed.

The invention thus provides methods for sterilization of pharmaceutical compositions.

Claims

1. A method of sterilising a pharmaceutical composition, comprising rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

2. A method according to claim 1, comprising increasing the temperature of the composition from the ambient temperature to the elevated temperature in less than 5 seconds.

3. A method according to claim 1 or 2, comprising decreasing the temperature of the composition from the elevated temperature to ambient temperature in less than 5 seconds.

4. A method according to any of claims 1 to 3, comprising heating the composition to an elevated temperature exceeding 130°C.

5. A method according to any of claims 1 to 4, wherein the period of time is less than 20 seconds and greater than 2 seconds.

6. A method according to any of claims 1 to 5, wherein the pharmaceutical composition comprises a drug in suspension, water or another solvent and, optionally, surfactants and/or preservatives.

7. A method according to claim 6 wherein the composition is a glucocorticosteroid composition, such as a budesonide suspension.

8. A method of treating a pharmaceutical composition to reduce its microbial load, comprising rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

9. A method according to claim 8, comprising maintaining the composition at or above the elevated temperature for a time necessary for sterilisation to be achieved.

10. A method of sterilising a concentrated formulation for use in a pharmaceutical composition, comprising rapidly heating the concentrated formulation from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the concentrated formulation to ambient temperature.

11. A method according to claim 10, comprising increasing the temperature of the composition from the ambient temperature to the elevated temperature in less than 5 seconds.

12. A method according to claim 10 or 11, comprising decreasing the temperature of the composition from the elevated temperature to ambient temperature in less than 5 seconds.

13. A method according to any of claims 10 to 12, comprising heating the composition to an elevated temperature exceeding 130°C.

14. A method according to any of claims 10 to 13, wherein the period of time is less than 20 seconds and greater than 2 seconds.

15. A method according to any of claims 10 to 14, wherein the concentrated formulation is selected from

a pharmaceutical agent and a surfactant;
a suspension of a drug in a surfactant solution; and
a suspension of a drug in water or another solvent.

16. A method of sterilising a pharmaceutical composition, characterized in that:-

the sterilization is carried out by "square wave heating"; and
the sterilization is carried out continuously.

17. A method according to claim 16, wherein square wave heating comprises rapidly heating the pharmaceutical composition from ambient temperature to an elevated temperature, maintaining it at or above the elevated temperature for a period of time, and rapidly cooling the pharmaceutical composition to ambient temperature.

18. A method according to claim 16 or 17, further comprising dispensing sterilized pharmaceutical composition into storage vessels and sealing the storage vessels in a continuous process.

19. A method according to claim 18 wherein dispensing is by the "blow-fill-seal" method.

20. A method according to any of claims 18 to 19, wherein the storage vessels are selected from pre-sterilised ampoules, typically of polymeric material, metal or glass.

21. A method according to any of claims 18 to 20, optionally comprising diluting a sterile concentrate by a bulk composition under sterile conditions prior to dispensing into storage vessels.

22. A pharmaceutical composition sterilised by a method according to any of claims 1 to 21.

23. A pharmaceutical composition sterilised by a "square wave heating" process.

24. A suspension of budesonide sterilized according to the method of any of claims 1 to 21.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L2/00 A61L2/04 A61K31/56 C07J5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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